21. (Amended) The formulation of claim 16, wherein said botulinum toxin is of a botulinum toxin ~~serotype~~ type selected from the group consisting of ~~serotypes~~ Types A, B, C_1, C_2, D, E, F and G.

Remarks

Claims 1-28 are presently pending in this application.

Claim Amendments

Claim 2 has been amended to correct an obvious misspelling of the word "centigrade" and for no other reason.

Claims 7 and 21 have been amended to maintain consistency between these claims and the claims depending from them. The word "serotype" has been amended in favor of the word "type" in these instances.

Applicants do wish to draw the attention of the Examiner to the Annals of Internal Medicine reprint supplied and listed on the accompanying PTO form 1449, which is to clarify that serotype and type have the same meaning in the context of the present application. They both refer to the antigenically distinct forms of toxin produced by Clostridium botulinum. The term "strain" is usually applied to varieties of the bacteria itself that produce the types (or serotypes) of botulinum toxin in varying yields.

The Examiner is thanked for pointing out the inconsitency in word choice between the claims 7 and 8 and 20 and 21 and for suggesting the insertion of the word "of" after the second occurrence of the "botulinum toxin" in claims 8 and 21.

Rejection under 35 U.S.C. 112, First paragraph

The Examiner has rejected claims 1-8, 12-22 and 25-28 of the invention as lacking enablement to allow claims to a pharmaceutical formulation comprising a botulinum toxin other than type B. She provides an analysis of the Wands factors for the proposition that it provides factors for analysis in determining when a disclosure for a patent application requires undue experimentation. The Examiner thus concludes that the factors presented prove that "undue experimentation would have been required by one of

ordinary skill in the art to reproducibly practice the full scope of the present invention as claimed." The Prevot reference (as cited in the Office Action and supplied by Applicants as a translation from the original in French) is cited that there are differences between the toxins in their preservation properties. The Prevot reference was published to survey the state of the art in 1953.

Applicants wish to point out that the amount of experimentation is only one of a lengthy list of factors that the Federal Circuit has presented in determining whether the scope of claims in an invention are enabled by the disclosure. The list of the factors to be considered are:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Further the court in Wands states:

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. In re Wands, 858 F.2d 731 at 737, 740, 8 USPQ2d 1400 at 1404, 1407.
>
> The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing

all the above noted factual considerations. 858 F.2d at 737, 8 USPQ2d at 1404

Applicants assert that the Examiner's rejection is improper for failing to take into account all the factors in reaching a conclusion that undue experimentation would be required to practice the invention in respect of types of Botulinum toxin other than type B, and further that Prevot reference is not useful in making an assessment of the state of the art as it is understood today. Prevot forwards the belief, that was held at an earlier period in time that some proteins are "autolytic" (see section 6 or Chapter IV at p.10). This along with the numerous instances of Prevot reporting throughout the monograph of the inconsistent behavior of the toxins under the same conditions of batches of the toxin demonstrates that the purification of the toxin from other cell components was not consistent or adequate. The state of the art today comprehends the need for rigorous purification from other cellular contaminants such as proteases which can attack and destroy the peptidic chains of the toxin. The specification in Section III at pages 10 – 13 teaches methods of purification of both Type A and Type B toxins to remove unwanted impurities that would adversely affect the long term stability of a toxin formulation.

The Examiner's comment that Prevot teaches the preservation of toxin types C and D is independent of pH is not fully understood, since this would indicate that these toxins would work well within the pH range of 5 to 6 taught by the invention. Prevot also teaches that type B toxin is rapidly degraded about pH 3.5 which is expressly disproved by the Applicant's working examples showing the superior stability of the type B toxin at pH 5 to 6. Applicant's assert the unpredictability postulated by the Examiner based on a reading of Prevot is largely due to the poor purification of the enzymes that could be accomplished using the technologies available in the late 40's and early 50's. The Applicant's have provided extensive teaching regarding the purification of toxin in preparing it for formulation into the stable solutions. Isolation of types A and B are described in detail in the specification and one skilled in the art would understand how to adapt the disclosed methods to provide purified amounts of types C – G from reading the specification and references available prior to the filing of this application.

In In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated: [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Therefore, Applicants believe that they are entitled to the full scope of the claims as they presently stand.

In answering the assertion that undue experimentation would be required the Applicants point to case law that has decided that :

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

The Applicants have provided detailed guidance with respect to the isolation and purification of botulinum toxins and the subsequent formulation of the various types to provide stable liquid formulations. The fact that the working examples provide instances of production of type B is not sufficient to require limitation of the claims to type B, since one of ordinary skill in the art would understand how to apply the teaching to

formulations of other toxin types, and even though some experimentation might be required in order to make formulations of other toxins types, the amount of experimentation is not undue since adequate guidance is provided and since the experimentation required is routine and within the ordinary skill level of a protein formulation specialist.

For the reasons set forth above it is believed that this case is now in condition for allowance. Reconsideartion and allowance are respectfully solicited.

Respectfully submitted,

Date: 20 APR 01

SIGNATURE OF PRACTITIONER

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